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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,162	03/16/2001	Manuela Martins-Green	407E-000500US	5788

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,162	MARTINS-GREEN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-8,19 and 87-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,7,19,87,88,90,92 and 93* is/are rejected.

7)☒ Claim(s) *8,89 and 91* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment filed 25 October 2002 (Paper No. 13) has been entered in full. Claims 2, 5, 9-18 and 20-86 were cancelled.

The Declaration of Dr. Manuela Martins-Green filed under 37 CFR 1.132, filed 18 November 2002 (Paper No. 14) has been entered.

The information disclosure statement filed 04 November 2002 (Paper No. 15) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The amendment filed 09 January 2003 (Paper No. 16) has been entered in full. Claims 1, 3, 4, 6, 7, 8, 19, 87-93 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection of claims 6-8 as set forth at page 3 of the previous Office Action (20 May 2002, Paper No. 11) is *withdrawn* in view of the amendment (25 October 2002, Paper No. 13).

The rejection of claim 1 under 35 USC 112, first paragraph, as set forth at pages 3-7 of the previous Office Action (20 May 2002, Paper No. 11) is *withdrawn* in view of the Martins-Green Declaration (18 November 2002, Paper No. 14). The Martins-Green Declaration filed under 37 CFR 1.132 was sufficient to overcome the 35 USC 112, first

paragraph rejection of claim 1 drawn to a polypeptide comprising a single interleukin-8 (IL-8) fragment, wherein said IL-8 fragment stimulates the differentiation of fibroblast to myofibroblasts, and wherein said fragment comprises an ELR motif, and is no greater than about 15 amino acids in length.

Claim Rejections – 35 USC § 112, first paragraph, enablement

Claims 3, 87 and 93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabling for claims drawn to the polypeptide of claim 1, wherein the polypeptide in not angiogenic and the polypeptide of claim 1, wherein the polypeptide is a cyclic polypeptide. The basis for this rejection is set forth at pages 3-7 of the previous Office Action (20 May 2002, Paper No. 11).

The specification is not enabling for IL-8 fragments that comprise the ELR motif which are not angiogenic. Applicant is claiming an unproven activity of IL-8 fragments. The art teaches (IDS submitted by Applicant, Paper No.14, reference#3) that members of CXC chemokines, which contain the ELR motif, are potent promoters of angiogenesis. The experiments of Dr. Martins-Green did not demonstrate that the IL-8 peptides (comprising the ELR motif) were not angiogenic.

The specification is not enabling for cyclic peptides. The experimentation is undue because one skilled in the art cannot readily anticipate the effects of the

biological activity of cyclic IL-8 peptides versus its linear counterpart. The specification fails to consider the dynamics of protein folding and the effect on receptor binding. The literature suggests that regions directly involved in binding and in providing the correct three-dimensional spatial orientation of binding and active sites are critical to the protein's structure/function relationship (Ngo *et al.*).

Due to the large quantity of experimentation necessary to generate cyclic IL-8 peptides and screen same for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of protein folding on structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections – 35 USC § 112, second paragraph

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is set forth at page 7 of the previous Office Action (20 May 2002, Paper No. 11).

Applicant's arguments have been fully considered. Applicant states that the specification defines the N-terminal fragment to be a polypeptide fragment that has an amino acid sequence present in the N-terminal half of a larger polypeptide and that the limitations of claim 1 are incorporated into claims 6 and 7.

Applicant's arguments are not found persuasive because it is unclear which amino acids are being encompassed in the N-terminal fragment. The recitation of percent identity without reference to a single defined sequence is indefinite. The instant specification teaches two forms of IL-8, each with a different N-terminus. The definition of "N-terminal fragment" disclosed in the specification is a relative term. The IL-8 protein is over 60 amino acids long. "N-terminal fragment" can encompass any 15 amino acid stretch that comprises the ELR motif starting with residue 1 up to about residue 35. In addition, there is more than one ELR. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 88 and 90 are rejected under 35 U.S.C. 102(b) as being anticipated by Stern *et al.*, US Patent No. 5,641,867.

The instant claims are drawn to a polypeptide comprising a single interleukin (IL-8) fragment, wherein, said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said fragment comprises an ELR motif, and is no greater than about 15 amino acids in length. Stern teaches a peptide derived from the

ELR-region of IL-8 (SEQ ID NO:17). The peptide of Stern comprises the ELR motif and is 12 amino acids long. Stern teaches an IL-8 fragment which comprises the amino acid sequence of SEQ ID NO:8 and is 100% identical. Stern teaches an IL-8 fragment which comprises the amino acid sequence of SEQ ID NO:9 and is 100% identical (column 21, lines 55-57 and column 41-42 and sequence query, Appendix A and B). The peptide of Stern is expected to have the activity of stimulating the differentiation of fibroblasts to myofibroblast because a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Furthermore, the peptide of Stern (SEQ ID NO:17) is one amino acid longer than SEQ ID NO:9 and the instant specification does not provide a description of how one amino acid would create a tangible difference in claimed the composition and those peptides in the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stern *et al.*, US Patent No. 5,641,867 in view of Gosselin *et al.*, US Patent 5,900,235.

The teachings of Stern are described above. Stern does not teach a composition comprising a single interleukin (IL-8) fragment, wherein, said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said fragment comprises an ELR motif, and is no greater than about 15 amino acids in length and a pharmaceutically acceptable carrier.

Gosselin teaches the therapeutics uses of IL-8 (abstract; column 1, lines 5-11 and column 8, lines 53-67). Gosselin teaches pharmaceutically or physiologically acceptable, therapeutically effective amounts of an IL-8 agent (column 4, lines 15-20). Gosselin teaches that IL-8 agents includes IL-8 (72 or 77 amino acid form), derivatives and analogs of IL-8 and modified peptides showing significant biological activity analogous to that of IL-8 in various biological systems (column 5, lines 40-52).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the instant invention of a composition comprising an IL-8 fragment and a pharmaceutically acceptable carrier. The motivation and expected success is provided by Stern who teaches the fragment and Gosselin who teaches the importance of IL-8 in biological activities and its uses in various treatments.

Claim Objections

Claims 8, 89 and 91 are objected to for depending from a rejected claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
March 17, 2003